

PAPER

How useful is [^{123}I] β -CIT SPECT in clinical practice?

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Objective: To assess the accuracy and clinical usefulness of [^{123}I] β -CIT (2 β -carbomethoxy-3 β -(4-iodophenyl)tropane) SPECT in the differential diagnosis of Parkinson's disease.

Subjects: 185 consecutive patients with symptoms of movement disorder were studied. The diagnoses were Parkinson's disease (92), essential tremor (16), vascular parkinsonism (15), various Parkinson plus syndromes (P+) (12), dementia with Lewy bodies (DLB) (5), dystonia (5), drug induced movement disorder (12), and other diagnoses (8). A reference group (psychogenic parkinsonism) comprised 20 subjects with complaints suggesting extrapyramidal disease but with no unequivocal signs on clinical examination and no abnormalities on brain imaging.

Results: β -CIT uptake was significantly lower in the whole striatum as well as separately in the putamen and in the caudate nucleus in Parkinson's disease than in the reference group or in drug induced movement disorder, essential tremor, or dystonia. The uptake of β -CIT in the vascular parkinsonism group was heterogeneous and mean β -CIT uptake fell between the reference group and the Parkinson's disease group. In the P+ and DLB groups the striatal uptake ratios overlapped those of the Parkinson's disease group.

Conclusions: [^{123}I] β -CIT SPECT may not be as useful a tool in the clinical differential diagnosis of Parkinson's disease as was previously believed, but it was 100% sensitive and specific for the diagnosis in younger patients (age <55 years). In older patients (age >55 years) specificity was substantially lower (68.5%). This differential specificity reflected the different distribution of differential diagnostic disorders (P+, DLB, vascular parkinsonism) in the older and younger age groups.

The main symptoms of idiopathic Parkinson's disease—resting tremor, rigidity, bradykinesia, and postural instability—are mostly caused by degeneration of dopaminergic neurones projecting from the substantia nigra to the caudate and putamen. However, similar symptoms are also caused by other mechanisms, with or without nigrostriatal pathology. It is beneficial, although not always easy, to differentiate patients with early stage Parkinson's disease from those with other types of movement disorder.

Dopamine transporters (DAT) are dopamine reuptake proteins on the presynaptic terminals of dopaminergic neurones.¹ Measuring DAT density by using DAT ligands and single photon emission computed tomography (SPECT) or positron emission tomography (PET) provides in vivo information on the integrity of these presynaptic terminals. [^{123}I] β -CIT (2 β -carbomethoxy-3 β -(4-iodophenyl)tropane) is a cocaine derivative radioligand which binds to dopamine transporters with substantial striatal specificity at 24 hours postinjection.²

In idiopathic Parkinson's disease, reduced striatal DAT density is caused by a reduction in the number of neurones projecting from the substantia nigra to the striatum, particularly the putamen^{3–5}; the number of DATs per neurone may also be lower than normal because of the attempt to increase the amount of synaptic dopamine by reducing the reuptake.³ Many studies have shown that [^{123}I] β -CIT SPECT is helpful in the diagnosis of Parkinson's disease.^{6–12} There is also a correlation between the reduction in β -CIT uptake and the severity of Parkinson's disease.^{6–7, 9–12, 13} In unilateral Parkinson's disease the reduction in β -CIT binding is more evident in the contralateral striatum, but binding in the ipsilateral striatum is usually also lower than in healthy controls, suggesting that β -CIT SPECT can detect preclinical Parkinson's disease.^{14–15}

A few reports have suggested that β -CIT SPECT might be useful in the differential diagnosis of Parkinson's disease and

the so called "Parkinson plus" syndromes (P+)—for example, progressive supranuclear palsy (PSP) and multiple system atrophy (MSA)—but more recent ones have failed to do so.^{16–19} [^{123}I] β -CIT SPECT imaging of these patients has shown a decrease in overall DAT density, but the radiotracer uptake pattern may also be different from Parkinson's disease, the striatum being more uniformly affected.

In healthy subjects, ^{123}I - β -CIT uptake decreases with age, the reduction varying from 3.3% to 10% per decade.^{6, 20–22} However, to our knowledge there have been no studies on whether the age of the population affects the diagnostic accuracy of this method. Decreased [^{123}I] β -CIT uptake has been reported in dementia with Lewy bodies (DLB), sporadic olivopontocerebellar atrophy, and Wilson's disease.^{23–26} No significant reduction in DAT density has been found in patients with dopa responsive dystonia, idiopathic cervical dystonia, or essential tremor.^{27–29}

The sensitivity and specificity of a diagnostic test in the classical sense is calculated between two strictly predefined groups. However, such conditions very rarely exist at the clinic. Our aim in this study was rather to evaluate the potential of β -CIT SPECT as a clinician's differential diagnostic aid.

METHODS

Subjects and clinical assessment

We studied 185 patients (83 women and 102 men), all consecutive referrals to the outpatient clinic of the department of neurology of Helsinki University Central Hospital from 1996 to 1998 with suspicion of striatal pathology, based

Abbreviations: CIT, carbomethoxy-3 β -(4-iodophenyl)tropane; DAT, dopamine transporters; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; ROC, receiver operating characteristic; ROI, region of interest; SPECT, single photon emission computed tomography

on the clinical history and neurological examination. The mean age of the patients was 59.9 years (range 29 to 84), and the mean duration of symptoms was 3.4 years (range 1 to 30). Hoehn and Yahr and Schwab–England scales were used to assess the disease stage in Parkinson's disease. MRI or CT, or both, were carried out in all patients. The most likely clinical diagnosis was made separately by two neurologists (JL and SK) based on standard clinical criteria,^{30–33} a clinical follow up of at least two years after SPECT imaging, and the MRI and CT findings. No necropsies were done. The study was approved by the ethics committee of the Department of Neurology, Helsinki University Central Hospital.

Ninety two patients had Parkinson's disease, 16 had essential tremor, 15 had a movement disorder of vascular origin (with either a focal vascular lesion in the basal ganglia area or general leukoaraiosis, or both; a typical clinical picture; and resistance to antiparkinsonian drug treatment), five had probable DLB, and five had cervical or other type of focal dystonia. Eight patients had MSA and four had PSP, and these were grouped as a P+ group in the statistical analysis. Twelve patients had a drug induced movement disorder, neuroleptics being the cause in all except one patient who was taking lithium.

A reference group was formed of 20 subjects who had fears or complaints suggesting an extrapyramidal disease, but in whom neither unequivocal signs on clinical examination nor abnormalities on CT or MRI were present. Eleven of these were diagnosed as having a somatoform disorder with subjective Parkinson's disease-like symptoms (psychogenic parkinsonism). Nine similar patients were not evaluated by a psychiatrist and were therefore not officially diagnosed as having somatoform disorder, but we considered all 20 to have psychogenic parkinsonism. Striatal dysfunction was not confirmed even at clinical follow up, and during the follow up the symptoms resolved. The numerical data on these subjects were used only descriptively to demonstrate the normal performance of our imaging system and were not used for testing statistical significance, as they are not an optimal control group. A control group of healthy volunteers could not be used because of radiation safety issues.³⁴ Eight cases (Alzheimer's disease, cervical disc prolapse, neurosyphilis, normal pressure hydrocephalus, sequelae of radiculitis, post-traumatic extrapyramidal symptoms, and two cases with unspecified ataxia) not fitting into any of the above groups were excluded from the statistical analysis and these are also not included in the tables.

The patients took their normal drug treatment on the day of scanning, as previous studies have shown that dopamine

agonists, l-dopa, and selegiline have no significant effect on β -CIT results.^{35, 36}

SPECT imaging and analysis

SPECT imaging was done 24 hours after an intravenous injection of [^{123}I] β -CIT (185 MBq on average) using a Picker Prism 3000XP triple head gamma camera with a low energy, ultrahigh resolution fan beam collimator (resolution 6.7 mm at 10 cm distance). Thyroid uptake was blocked by 400 mg of oral potassium perchlorate before the tracer injection. Data were reconstructed using a ramp filter and three dimensional post-filtering with a low pass filter. Chang attenuation correction was carried out and 4.4 mm thick transaxial slices were reformatted to the orbitomeatal line.

Regions of interest (ROI) were drawn on the striatum and separately on the caudate and putamen by employing a predefined ROI map, the shape and rotation of which was adjusted for each measurement, and counts per pixel values were calculated for each ROI. An ROI drawn on the cerebellum was used as reference (fig 1). The striatal [^{123}I] β -CIT uptake was expressed as the mean striatal counts divided by cerebellar mean counts.

Statistics

The non-parametric Spearman's rank correlation test was used to calculate correlations. Parametric analysis of variance was used to analyse the statistical significance of the difference in means between the various diagnostic groups, where a probability (p) value of <0.05 was considered significant. We used analysis of variance (ANOVA) to control the effect of multiple comparisons. The sensitivity and specificity of [^{123}I] β -CIT imaging for differentiating between the diagnostic groups was calculated in a 2 \times 2 contingency table, where sensitivity was defined as the proportion of test positive cases of all Parkinson's disease positive cases, and specificity was defined as the proportion of test negative cases of all Parkinson's disease negative cases. The cut off points were calculated using an ROC analysis, calculating the area under the ROC curve directly by extended trapezoidal rule and by a Wilcoxon type method with a confidence interval.

RESULTS

Demographics

Demographic data are presented in table 1. At the time of imaging, 39 patients (42%) with Parkinson's disease were receiving antiparkinsonian drugs (monotherapy or combination), as were six patients (50%) in the P+ group. Neither the

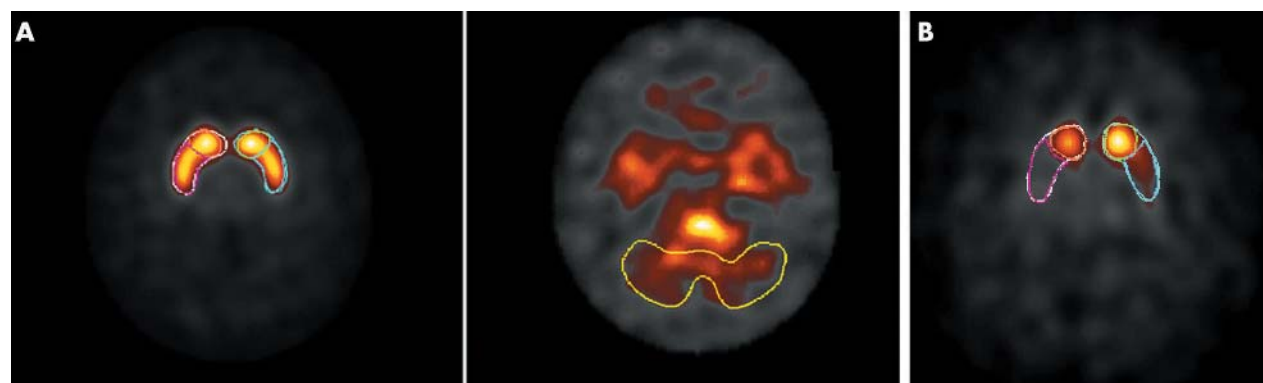


Figure 1 (A) Normal striata visualised by [^{123}I] β -CIT SPECT. The ROIs used were the whole striatum as well as the putamen and the caudate nucleus separately. Cerebellum was used as a reference region. (B) Striata of a Parkinson's disease patient. Note the interstitial asymmetry and predominance of putaminal degeneration.

Table 1 Demographic characteristics of the 177 subjects

	Diagnostic group							
	PD (n=92)	P+ (n=12) *	DLB (n=5)	VP (n=15)	Dystonia (n=5)	DIP (n=12)	ET (n=16)	Psy (n=20)
F/M (n)	41/51	6/6	2/3	7/8	1/4	5/7	8/8	8/12
Mean age (y)	59.4	65.4	69.0	70.7	51.0	62.6	53.9	53.1
Age range (y)	31.8 to 78.8	54.6 to 77.4	55.1 to 76.9	48.5 to 82.1	38.1 to 66.7	43.8 to 84.2	35.1 to 74.3	29.2 to 77.8
Duration of symptoms (y)	2.8 (2.8)	4.5 (3.9)	2.0 (0.7)	2.1 (1.9)	11.3 (13.0)	7.0 (2.1)	4.3 (5.0)	4.9 (5.8)
L-dopa	31 (34%)	5 (42%)	1 (25%)	4 (36%)	–	1 (8%)	2 (11%)	–
Dopamine agonist	6 (6.5%)	1 (8%)	–	–	–	1 (8%)	–	1 (4.5%)
Selegiline	9 (11%)	1 (8%)	–	–	–	–	–	1 (4.5%)
Anticholinergic	3 (3%)	–	–	1 (7%)	–	2 (17%)	–	–
Amantadine	5 (5.4%)	1 (8%)	–	–	–	–	–	–

*Parkinson+ group included four patients with progressive supranuclear palsy and eight with multiple system atrophy.

DIP, drug induced parkinsonism; DLB, dementia with Lewy bodies; ET, essential tremor; F, female; M, male; n, number of cases; P+, Parkinson plus syndromes; PD, Parkinson's disease; Psy, reference cases with psychogenic parkinsonism; VP, vascular parkinsonism; y, years.

age of the Parkinson group nor the duration of symptoms differed significantly from those of the other groups. The mean age of P+, DLB, and vascular parkinsonism groups was highest (>65 years).

Striatal β-CIT uptake in the subject groups

Mean [¹²³I]β-CIT uptake ratios of all subject groups in contralateral and ipsilateral ROIs (striatum, putamen, caudate) are presented in table 2. In addition, each subject's individual values of β-CIT uptake in the contralateral striatum are shown in fig 2. These data show significantly lower β-CIT uptake ratios in patients with Parkinson's disease than in those with drug induced parkinsonism, essential tremor, or dystonia, both in the whole striatum and separately in the putamen and the caudate nucleus. In the P+ and DLB groups the DAT densities overlapped those of the Parkinson's disease group. The caudate to putamen ratio seemed to be higher in some cases of Parkinson's disease than in the P+ or DLB groups, but the differences were not significant. Both P+ and DLB groups differed significantly from drug induced parkinsonism, essential tremor, or dystonia ($p<0.001$). The uptake of β-CIT in vascular parkinsonism was heterogeneous, and the mean DAT density fell between that found in psychogenic parkinsonism, essential tremor, dystonia, and drug induced parkinsonism and that in the Parkinson's disease group. In vascular parkinsonism the mean uptake ratios in the whole striatum, caudate, and putamen were significantly higher than in Parkinson's disease but lower than in drug induced parkinsonism, essential tremor, dystonia, or psychogenic parkinsonism (fig 2).

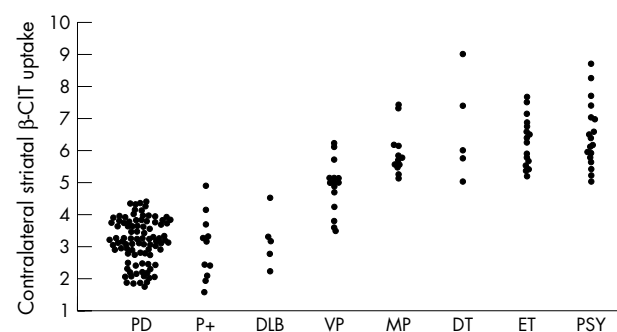


Figure 2 [¹²³I]β-CIT uptake in the striatum contralateral to the more severely symptomatic side in different patient groups. DLB, dementia with Lewy bodies; DT, dystonia; ET, essential tremor; MP, medication induced extrapyramidal syndrome; P+, Parkinson plus syndromes; PD, Parkinson's disease; PSY, reference cases with psychogenic parkinsonism; VP, movement disorder of vascular origin.

Correlation with severity of symptoms

In the Parkinson's disease group, the decrease in regional striatal β-CIT binding was correlated with symptom severity ($p<0.01$). There was a significant correlation between the Hoehn and Yahr stage and β-CIT uptake in the whole striatum on both the contralateral and the ipsilateral side, or in the putamen and caudate ROIs. In patients with Hoehn–Yahr stage I the reduction in β-CIT uptake was more prominent in the contralateral side, but a decrease in average ipsilateral DAT density was also evident (–36.8% compared with the referent cases with psychogenic parkinsonism). Striatal β-CIT uptake also correlated with the Schwab and England scores in the whole striatum, caudate, and putamen on the contralateral and ipsilateral sides. Overall, the correlations with Hoehn–Yahr and Schwab and England scores were consistently mildly stronger in the ipsilateral side than in the contralateral side. In other words, the better preserved striatum seemed to determine the patient's functional capacity rather than the more severely affected side.

The effect of age on β-CIT uptake

In non-parkinsonian subjects (psychogenic parkinsonism, essential tremor, dystonia, and drug induced extrapyramidal syndrome), β-CIT uptake correlated negatively with age ($r = -0.39$, $p<0.01$). The age related decline in this group was 3.7% in a decade.

In the Parkinson's disease group the reduction in striatal β-CIT uptake did not correlate significantly with age ($r = -0.18$, $p = 0.08$) (fig 3).

Sensitivity and specificity for Parkinson's disease

Sensitivity and specificity were analysed to address the question of how β-CIT SPECT differentiates idiopathic Parkinson's disease from other conditions. The cut off limit for a positive test result (uptake indicating striatal pathology) in each ROI was calculated by the ROC analysis with emphasis on high sensitivity. The sensitivity and specificity in Parkinson's disease diagnosis in both the contralateral striatum (as a whole) and the contralateral putamen were 98.9% and 80.5%, respectively. Overall, the uptake ratios in the contralateral striatum and putamen yielded better sensitivity and specificity than those in the caudate nucleus (table 3).

The specificity was substantially higher in subjects younger than 55 years than in those older than 55 years. The age cut off limit of 55 years was arbitrary and best divided our material into good and poorer specificity.

In patients aged less than 55 years, both sensitivity and the specificity were 100% when the contralateral striatal/cerebellar uptake ratio cut off was set at 4.5, and also 100% in the

Table 2 Striatal [123 I] β -CIT binding in the subject groups

	PD (n=92)	P+ (n=12)	DLB (n=5)	VP (n=15)	DIP (n=12)	Dystonia (n=5)	ET (n=16)	Psy (n=20)
Str _{contra}	3.2 (0.7)	3.4 (1.3) NS	3.2 (0.9) NS	4.9(0.7)***	5.9(0.8)***	6.7(1.9)***	6.2(0.8)***	6.5 (1.0)
Str _{ipsi}	3.7 (0.8)	3.7 (1.3) NS	3.5 (0.8) NS	5.6(0.7)***	6.0(0.8)***	6.8 (1.9)**	6.4(0.9)***	6.7 (1.1)
CaU _{contra}	4.4 (1.1)	4.5 (1.7) NS	4.0 (1.1) NS	6.2 (1.0)**	7.1(1.2)***	8.4 (1.6)***	7.6(0.9)***	7.6 (0.9)
CaU _{ipsi}	5.0 (1.1)	5.0 (1.5) NS	4.5 (1.0) NS	6.9 (0.9)***	7.3(1.2)***	8.7(1.7)**	7.8(0.9)***	7.8 (0.9)
Put _{contra}	2.4 (0.5)	2.9 (1.4) NS	2.8 (1.0) NS	4.4(1.1)***	5.7(0.7)***	6.4(1.1)***	6.1(0.9)***	6.3 (1.2)
Put _{ipsi}	2.9 (0.8)	3.2(1.5) NS	3.1(1.0) NS	5.1(1.0)***	6.0(0.8)***	6.7(1.2)***	6.3(0.9)***	6.6 (1.2)

Values are mean (SD).

Parkinson+ group includes four patients with progressive supranuclear palsy and eight with multiple system atrophy.

** $p < 0.01$, *** $p < 0.001$ v Parkinson's disease (unequal n honest significance post hoc test after ANOVA).

Cau, caudate; contra, contralateral to the clinically more affected side; DIP, drug induced parkinsonism; DLB, dementia with Lewy bodies; ET, essential tremor; ipsi, ipsilateral to the more affected side; P+, Parkinson plus syndromes; PD, Parkinson's disease; Psy, reference cases with psychogenic parkinsonism; Put, putamen; Str, striatum; VP, vascular parkinsonism.

contralateral putamen with the putamen/cerebellar cut off value of 3.1.

In patients over 55 years, the sensitivity was 98.4% and specificity 68.5% using the same cut off value of 4.5. Uptake measured from the putamenal ROI yielded 100% sensitivity and 68.5% specificity using a cut off value of 3.9.

The corresponding positive predictive values of the contralateral striatal/cerebellar β -CIT uptake ratio were 0.82 in the whole series, 1.0 in the age group 55 years or younger, and 0.77 in patients older than 55 years, and for the contralateral putamenal/cerebellar ratio, 0.58, 1.0, and 0.54, respectively.

DISCUSSION

Generally, a high β -CIT uptake value excludes presynaptic nigrostriatal Parkinson's disease, but leaves open the possibility of various other disorders, for example essential tremor. Midrange uptake values are problematic, not necessarily ruling out either parkinsonism in its various forms or vascular degeneration. Low uptake values are most common in Parkinson's disease, but exclude neither the so called Parkinson plus syndromes nor vascular degeneration. Thus the impact of β -CIT for the initial diagnosis of movement disorders is quite complex.

Our patients were referred for [123 I] β -CIT SPECT consecutively, not on predefined selection criteria as in most previous studies. We think that in such a setting we can better address the problem of how useful it is to measure DAT density with β -CIT in the diagnosis of Parkinson's disease in a specialist outpatient clinic.

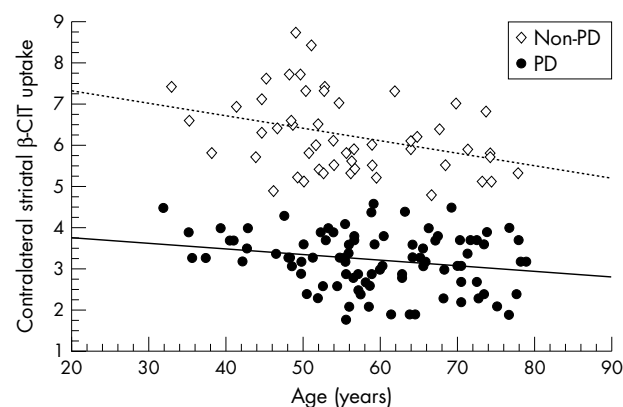


Figure 3 Correlation of DAT density with age in non-parkinsonian conditions and in Parkinson's disease. DAT density declined mildly with age in non-parkinsonian individuals (only psychogenic parkinsonism, essential tremor, dystonia, and drug induced extrapyramidal syndrome were included in the non-Parkinson's disease plot).

Some of the patients were on drug treatment and took their medication normally on the day of the scan. A small effect of medication on DAT binding was seen in a study using a different tracer and PET,³⁷ but previous studies have found that dopamine agonists, l-dopa, and selegiline had no significant effect on β -CIT SPECT results.^{35–36} A minor influence of medication on our scans cannot be entirely ruled out but it is highly unlikely to be significant. Some patients with essential tremor, drug induced parkinsonism, and vascular parkinsonism were also taking antiparkinsonian drugs on trial at the time of the scan, but none of them had a positive response.

Clinical follow up for at least two years after the scanning was used to confirm the clinical diagnosis. The diagnosis and differential diagnosis of Parkinson's disease are usually accurate when made by an experienced specialist. Most initially atypical cases show typical presentation in two to four years of follow up. We therefore believe that our clinical classification is reliable. Most cases of Parkinson's disease were correctly classified clinically at the first examination, and in these cases the information from [123 I] β -CIT SPECT was not significant for the diagnosis. Thus we do not recommend [123 I] β -CIT SPECT as a first line routine investigation for patients with parkinsonism. However, here it had an important role in patients with drug induced movement disorders, in some cases with psychiatric disease, and in a few cases where the diagnosis remained uncertain, as in those cases at least idiopathic Parkinson's disease could be ruled out.

The Parkinson's disease group showed a marked reduction in β -CIT uptake compared with the reference group in the whole striatum as well as in the putamen and caudate ROIs, in line with previous studies.^{6–12} The striatal β -CIT uptake ratios of the patients with dystonia, drug induced parkinsonism, or essential tremor were similar to those of the reference group with psychogenic parkinsonism and significantly different from those of the patients with Parkinson's disease, indicating that these conditions can be distinguished from Parkinson's disease using this method.

β -CIT uptake could not distinguish P+ syndromes and DLB from Parkinson's disease, as the DAT density was also reduced in these conditions. The difference between the β -CIT uptake in Parkinson's disease and P+ or DLB was neither significant in the whole striatum nor in the caudate nucleus and putamen separately. While some previous studies have suggested that there may be a difference in the caudate to putamen ratio between Parkinson's disease and P+ or DLB groups, others have not found any difference.^{16–19} There was no significant difference in the caudate to putamen ratio between these groups in our material, in line with most previous studies. In other words, by using β -CIT SPECT these three conditions can be differentiated from controls, and from cases of essential tremor, drug induced parkinsonism,

Table 3 Sensitivity and specificity of [123 I]β-CIT SPECT in the diagnosis of Parkinson's disease

	All		<55 years		≥55 years	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Str _{contra}	98.9	80.5	100	100	98.4	68.5
Str _{ipsi}	93.5	79.3	100	92.9	92.2	70.4
Cau _{contra}	93.5	74.7	100	96.4	90.6	63.0
Cau _{ipsi}	92.4	74.7	100	89.3	93.8	59.3
Put _{contra}	98.9	80.5	100	100	100	68.5
Put _{ipsi}	96.7	81.6	100	96.4	96.9	72.2

Cau, caudate; contra, contralateral to the clinically more affected side; ipsi, ipsilateral to the more affected side; Put, putamen; Str, striatum.

and dystonia, but not from each other. Another indication for β-CIT is to differentiate DLB or Parkinson's disease with dementia from Alzheimer's disease.³⁸

β-CIT uptake in the patients with vascular parkinsonism was heterogeneous, with half the cases in the normal range and the other half within the reduced range (range 3.6 to 6.3). Similar findings were reported in a previous study by Gerschlag *et al.*³⁹ Their interpretation was that β-CIT could reliably discriminate between Parkinson's disease and vascular parkinsonism, but closer inspection of their data shows overlap between the normal and the pathological range. Our results are in agreement with those of Lorberboym *et al.*⁴⁰

Remarkable interstriatal asymmetry of DAT density, more typical of Parkinson's disease, could also be seen in some of our patients with vascular parkinsonism. In the MRI or CT scans from those asymmetrical cases a vascular lesion was seen in the corresponding basal ganglia region. In patients with degeneration of deep white matter without focal basal ganglia lesions, β-CIT uptake was essentially normal. "Vascular parkinsonism" is a concept including extrapyramidal syndromes caused either by general white matter degeneration or by focal striatal vascular events, or both. Differentiating an extrapyramidal syndrome caused by a focal striatal vascular lesion from Parkinson's disease by means of [123 I]β-CIT SPECT is not reliable without CT or MRI. However, the clinical picture is usually at least suggestive of vascular parkinsonism. White matter degeneration in the absence of striatal lesions does not seem to result in a significant decrease in DAT density.

It is of note that dopamine transporter imaging in drug induced parkinsonism has been reported previously in only a small number of cases. In the present study we were able to confirm the previous preliminary results of normal indices in this group.^{41–42}

The accuracy of [123 I]β-CIT SPECT in the diagnosis of Parkinson's disease was assessed by an ROC analysis. The whole striatum and the putamen contralateral to the symptoms were the most useful ROIs, with 100% sensitivity and 80.5% specificity; this is not surprising, as in idiopathic Parkinson's disease the neurones projecting from substantia nigra to putamen are typically more severely affected than those projecting to the caudate nucleus, and the striatal pathology contralateral to the clinically more affected side is more prominent. Patients with P+ were more severely affected and had had symptoms for longer than the Parkinson's disease group. Nevertheless, their striatal uptake of [123 I]β-CIT was not lower than in the Parkinson group. This reflects the complex presynaptic and postsynaptic pathology in the P+ group of disorders.

Our results indicate that the sensitivity and specificity of [123 I]β-CIT SPECT in Parkinson's disease diagnosis are markedly influenced by the age of the subjects studied. [123 I]β-CIT SPECT was 100% sensitive and specific in younger patients (age less than 55 years), whereas in older subjects

specificity was substantially lower. In non-parkinsonian subjects, striatal β-CIT uptake values illustrating the DAT density of the nigrostriatal dopaminergic nerve terminals correlated negatively with age. The age related decline in β-CIT uptake in this material was 3.7% per decade, which is concordant with previous reports.^{6–20–22} This decline, however, is not great enough to affect specificity. The age dependent difference in the diagnostic accuracy of β-CIT is probably explained by the different distribution of diagnoses in the old and the young. As the diagnoses that diminish specificity and are present in the older population (P+, vascular parkinsonism, and DLB) have similar β-CIT uptake ratios, using age corrected values would not increase the specificity. In younger subjects vascular parkinsonism and DLB, which also had reduced striatal DAT density, are rare. A patient younger than 55 with extrapyramidal symptoms is very likely to have Parkinson's disease if reduced DAT density is found in the striatum. However, most patients with suspected nigrostriatal pathology are older than 55. As the specificity for Parkinson's disease is substantially lower in this group, we conclude that measuring DAT density with β-CIT may not be clinically as useful as previously suggested.

It is also of value to be able to exclude or demonstrate presynaptic nigrostriatal pathology (including Parkinson's disease, P+, and DLB) and to differentiate these conditions from those without nigrostriatal presynaptic pathology, such as drug induced parkinsonism, essential tremor, psychogenic parkinsonism, and Alzheimer's disease. The specificity of β-CIT for differentiating conditions with known presynaptic pathology from those without such pathology is better than the specificity for Parkinson's disease diagnosis. The presence of vascular parkinsonism, especially at an older age, would diminish the specificity in this setting.

The unquestionable benefit of DAT imaging with β-CIT lies in the fact that it provides *in vivo* information on nigrostriatal degeneration, and a lowered β-CIT uptake correlates with symptoms rather than with age. Thus it may be used as an objective *in vivo* measure of disease progression in addition to clinical measures. Circumspection is necessary, however, as the DAT is subject to compensatory and pharmacological regulation. Patients with pure hemiparkinsonism already have a reduced β-CIT uptake on the side ipsilateral to the symptomatic side (in our material, −37% of reference values), which means that a decrease in β-CIT uptake can already be detected in the preclinical stages of disease. [123 I]β-CIT SPECT may therefore be used in clinical trials to detect Parkinson's disease very early or even presymptomatically as a cheaper and more readily available, though less reproducible,^{43–44} alternative to PET.

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